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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/692,811	10/20/2000	Stephen Donovan	17324	8867

7590 09/09/2003

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EXAMINER	
BUGAISKY, GABRIELE E	
ART UNIT	**PAPER NUMBER**
1653	6

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/692,811	DONOVAN, STEPHEN	
	Examiner	Art Unit	
	Gabriele E. BUGAISKY	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2-4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Information Disclosure Statement

Reference CI of paper #2 has not been considered. The citation is to a tome on internal medicine & the only specific pages supplied for consideration were the table of contents.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating specific endocrine disorders (growth hormone excess), hyperthyroidism (T3 excess), and Cushing's disease (ACTH excess) and using induction of amenorrhea using botulinum toxin by direct injection into specific loci with the hypothalamus and /or hyophysis., does not reasonably provide enablement for a method using any neurotoxin which is administered anywhere in the brain, in an unspecified amount and with an outcome whereby the method of determination is lacking. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). the issue of enablement in molecular biology was considered. There are eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working

examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. Although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable .First, the specification is directed solely to the use of botulinum toxin to treat endocrine disorders. Stereotactic delivery of specific substances to various regions of the brain is well established for animal models, however, it is not clear that such drug delivery in humans is considered as common- the potential benefit must far outweigh the risk of error of the procedure. Applicant has produced a single example each of treatment of acromegaly (growth hormone excess), hyperthyroidism (T3 excess) Cushing's disease (ACTH excess) and induced PL excess resulting in amenorhhea. With respect to the latter, the specification is silent as to whether unintended lactation occurred as a result of high circulating levels of prolactin. The Examples for contraception appear to be prophetic. Considering the toxicity of botulinum toxin, the Examiner can at best conclude that the Applicant has not enabled treatment of any endocrine disorder by intracranial injection of botulinum toxin, but only treatment of the specific endocrine disorders listed above by injection of botulinum toxin into the specific hypothalamic or hypophysic location described for each treatment milieu. There is no evidence on the record to support, e.g., that a treatment for GH overproduction is feasible by injection of botulinum toxin into any intracranial location other than the arcuate nucleus of the hypothalamus Indeed, VAN de KAR *et al.* showed that following hypothalamic injection of the neurotoxin 5, 7, dihydroxytryptamine that no change in basal ACTH, corticosterone, oxytocin, prolactin, renin and vasopressin levels were observed,; however, the injected animals showed an altered response to subsequent injection of the serotonin agonist 8-hydrosxy-2-(dipropylamino)tetralin in corticosterone , prolactin and

oxytocin. Therefore, not all endocrine hormone levels can be expected to respond in a similar fashion ; and it is likely that the specific site of administration also plays an important role in the response to a neurotoxin. Thus, it is suggested that the claims be amended to recite the specific disorder and location of injection. It is also suggested that the claims be amended to recite a therapeutically effective amount of the disclosed botulinum toxin, a manner of administration and a step to determine whether the desired outcome has been achieved. Although the art recognizes the use of botulinum toxin to block release of neurotransmitters, the claims encompass administration in any intracranial location in unspecified amounts without direction. Since many embodiments would be expected to be not only non-operative but also have unintended potentially lethal side effects, one of skill in the art has been given an invitation to experiment to determine an operative embodiment that may be successful for human treatment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites "in an amount of between about". The word "about" renders the claim indefinite since it is a relative term that has not been defined in the specification. The metes and bounds of the claim are thus unclear. It is also unclear whether the dosage is in units/ kg body weight or some other parameter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by MONTI *et al.* (reference CZ of the IDS of 10/2000). The reference shows that hypothalamic administration of atropine prevents hypergonadism in female hemicastrated rats. It is thus anticipatory for the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

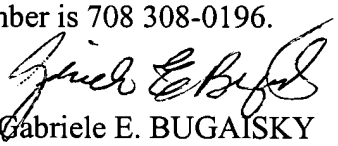
Claims 1-4, 6, 9-10, 13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsson *et al.* in view of ANDREWS. The Jacobsson reference teaches that botulinum toxin type F inhibits calcium stimulated GH release from rat pituitary cells and states in the final paragraph that their results suggest that VAMP is of importance for pituitary hormone secretion under physiological conditions and may be of clinical significance in, e.g., ; pituitary adenomas. ANDREWS discusses surgical treatment of pituitary adenomas and states

that stereotactic delivery of radioactive substances to ablate the tumor cells and decrease hormone levels is becoming increasingly successful. In order to avoid radiation and reduce GH secretion from GH secreting adenomas, it would have been obvious for one of skill in the art to use sterotactic delivery of botulinum toxin F directly to pituitary cells with the expected result that calcium stimulated GH release would be inhibited.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gabriele E. BUGAISKY whose telephone number is (703)308-4201. The examiner can normally be reached on 8:15 AM- 2 PM, Tu & Th, 8:15 AM-1:30 PM, We & Fr.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher SF Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are 703 308-4242 for regular communications and 703 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708 308-0196.



Gabriele E. BUGAISKY
Primary Examiner
Art Unit 1653

September 8, 2003